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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/662,199	09/12/2003	Francis Barany	19603/3641 (CRF D-933F)	9453

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EXAMINER

RAO, MANJUNATH N

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 04/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/662,199

Applicant(s)

BARANY ET AL.

Examiner

Manjunath N. Rao, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 February 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-8 is/are pending in the application.
- 4a) Of the above claim(s) 1-4, 7 and 8 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 5 and 6 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 12 September 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 9-12-03.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

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DETAILED ACTION

Claims 1-8 are currently pending and are present for examination. Claims 5-6 are now under consideration. Claims 1-4, 7-8 remain withdrawn from consideration as directed to non-elected invention.

Election/Restrictions

Applicant's election with traverse of Group III, Claims 5-6 in paper filed on 2-14-05 is acknowledged. The traversal is on the ground(s) that the Groups are all closely related and therefore coexamination of all Groups would not require independent searches. This is not found persuasive because while the searches for the four groups may overlap, they are not coextensive. Furthermore, as stated in the previous Office action, these groups are drawn to different methods involving different steps and different end-results.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-4 and 7-8 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in paper filed on 2-14-05.

Specification

Examiner notes that applicants have not updated the relationship of the instant application to its parent application 09/480515, that has been abandoned. Examiner urges applicants to amend said information in response to this Office action.

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5 and 6 claim depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 5 recites the phrase “oligonucleotides suitable for ligation”. It is not clear to the Examiner as to what applicants mean by the term “suitable” in the context of the above claim. Examiner suggests cancellation of the term which would eliminate the ambiguity without affecting the scope of the claim.

Claims 5 and 6 claim depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 5 recites the phrase s “denaturation treatment”, “thermal hybridization treatment” and “detecting the presence”. The metes and bounds of these phrases especially with reference to the conditions under which the above steps are practiced are not clear to the Examiner. Correction is required.

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The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting DNA by a cyclic reaction of annealing at about 50 degree C and denaturing at about 105 degree C and using a specific thermocyclable ligase enzyme having an amino acid sequence SEQ ID NO:2 or 8, wherein the detection is by gel electrophoresis of the reaction products, does not reasonably provide enablement for such a method comprising a cyclic reaction of annealing and denaturing at any temperature using any or all ligases including variants, mutants and recombinants and involving any or all methods of detecting the products. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 5-6 are so broad as to encompass the use of any ligase (claim 5) and any reaction conditions (i.e., annealing and denaturing temperatures) and any method of detecting the products formed. The scope of the claims is not commensurate with the enablement provided by

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the disclosure with regard to a method of detecting DNA comprising the use of any or all ligases, including variants, mutants and recombinants of SEQ ID NO:2 and 8, any or all reaction conditions and detection procedures broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a method comprising the use of polypeptide with SEQ ID NO:2 or 8 in a reaction condition comprising annealing/denaturing between 50 degrees and 105 degrees only and detection method comprising gel-electrophoresis only. It would require undue experimentation of the skilled artisan to practice the method using any ligase under any reaction condition and any method of detection of the product. The specification is limited to a method that comprises the use of SEQ ID NO: 2 and 8 as a ligase and reaction conditions associated with the use of the above two polypeptides but provides no guidance with regard to the method of detecting DNA comprising the use of any or all ligases, including variants, mutants and recombinants of SEQ ID NO:2 and 8, under any or all reaction conditions and detection procedures broadly encompassed by the claims. In view of the great breadth of the claim, amount of experimentation required to practice the method as claimed, the lack of guidance, working examples, and unpredictability of the art in predicting function and characteristics of a polypeptide from a polypeptide primary structure (e.g., see Ngo et al. in *The Protein Folding Problem and Tertiary Structure Prediction*, 1994, Merz et al. (ed.),

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Birkhauser, Boston, MA, pp. 433 and 492-495), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While enzyme isolation techniques, recombinant and mutagenesis techniques and general molecular biological techniques including DNA detection techniques are known, to practice a method as encompassed by instant claims, requires more guidance than that provided by the instant specification.

The specification does not support the broad scope of the claims which encompasses a method of detecting DNA comprising the use of 8 because the specification does not establish: (A) a universal method that can be performed using any or all ligases including the use of mutants, variants and recombinants under any reaction conditions; (B) does not provide any or all ligases including variants of SEQ ID NO:2 or 8 that can be used in the claimed method; (C) the general tolerance of ligases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue in a ligase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices of reaction conditions is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to practice the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method comprising the use of any or all ligases under any or all reaction conditions. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, the

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claimed method is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

Claims 5-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 5-6 are directed to a method comprising the use of ligase polypeptides including variants, mutants and recombinants of SEQ ID NO:2 or 8. Claims 5-6 are rejected under this section of 35 USC 112 because the claims are directed to a genus of polypeptides including those derived from SEQ ID NO:2 or 8 (including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue in SEQ ID NO:2 or 8 and fragments of SEQ ID NO:2 or 8) that have not been disclosed in the specification. No description has been provided of the modified polypeptide sequences encompassed by the claim. No information, beyond the characterization of SEQ ID NO:2 or 8 has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of the structure of all the polypeptide sequences derived from SEQ ID NO:2, including fragments and variants within the scope of the claimed genus. The genus of polypeptides for use in the claimed method is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these

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claims. The specification discloses only a two species of the genus for use in the claimed method which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 5 is rejected under 35 U.S.C. 102(b) as being anticipated by Landgren et al. (Science, 1988, Vol. 241 (4869):1077-1080) or Wu et al. (Gene Vol. 76 :245-254, 1989 cited in the IDS).

This rejection is based upon the public availability of a printed publication. Claim 5 of the instant application is drawn to a method of detecting a polynucleotide (DNA) using a ligase enzyme which ligates two single stranded DNA hybridized to another single strand DNA. The method involves subjecting the mixture of the DNAs to denaturation and hybridization treatments followed by detection of the ligated oligonucleotide DNAs.

Landgren et al. or Wu et al. indeed teach an identical method. Landgren et al. teach an assay to detect the presence of a given DNA based on the ability of two oligonucleotides to anneal immediately adjacent to each other on a complementary target DNA molecule which are then ligated by a DNA ligase provided that the nucleotides at the junction are correctly base-paired. The reference also states that such a method can be used rapid and standardized identification of genomic DNA (also see Figure 1 on page 1078) by denaturing, annealing (hybridizing) and ligating. The method disclosed by Landgren is identical to the method claimed in claim 5.

Wu et al. also disclose an identical method. In fact, applicants themselves admit that Wu et al. disclose such a method and is capable of amplifying the DNA starting with 500,000 copies in 95 hours, using 75 cycles of denaturing, annealing and followed by detecting (see page 4 of the specification). Therefore, Landgren et al. or Wu et al. anticipate claim 5 as written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Landgren et al. (Science, 1988, Vol. 241 (4869):1077-1080) or Wu et al. (Gene Vol. 76 :245-254, 1989 cited in the IDS) as applied to claim 5 above, and further in view of Takahashi et al. (J. Biol. Chem., 1984, Vol. 259(16):10041-10047).

Claim 6 in this instant application are drawn to a method of detecting a polynucleotide (DNA) using a ligase enzyme which ligates two single stranded DNA hybridized to another single strand DNA wherein the ligase is a thermocyclable ligase which does not become irreversibly denatured and lose its catalytic activity when subjected to temperatures ranging from 50 degree C to 105 degree C. The method involves subjecting the mixture of the DNAs to denaturation and hybridization treatments followed by detection of the ligated oligonucleotide DNAs.

The references of Wu et al. and Landgren et al. as it applies to claim 5 has already been discussed above. These two references teach an identical method of detecting a given DNA in a sample. However, both the references do not teach the use of thermocyclable ligase that can withstand temperatures ranging from 50 degree C to 105 degree C.

Takahashi et al. teach a thermocyclable ligase enzyme and its properties. Takahashi et al. teach the purification and properties of a DNA ligase isolated from *T.thermophilus* HB8 which is also known as *T.aquaticus* HB8 in the art and which is identical to the enzyme of the instant application and which exhibits identical thermostable properties.

With all the above three references in hand it would have been obvious to those skilled in the art to use the thermostable enzyme taught by Takashi et al. in the assays and detection reaction taught by Landgren et al. or Wu et al. One of ordinary skill in the art would have been motivated to do so since using the enzyme of Takahashi et al. would eliminate the requirement of replenishing the ligase enzyme after each cycle of denaturation and annealing. One of ordinary skill in the art would have a reasonable expectation of success since Takashi et al. provide the thermocyclable ligase and Landgren et al. or Wu et al. provide the basic ligase detection method.

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Therefore the above invention would have been *prima facie* obvious to one of ordinary skill in the art.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

A handwritten signature in black ink, appearing to read "Manjunath N. Rao". The signature is fluid and cursive, with a large initial "M" and a long, sweeping underline.

Manjunath N. Rao, Ph.D.

Primary Examiner

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April 20, 2005